

Preeclampsia and other placenta related pregnancy complications and future maternal cardiovascular health

- a tentative clinical follow-up flow chart



Student Project

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1 Introduction

This student project about preeclampsia and future maternal cardiovascular health is part of the student program at the Medical School of Oslo University, Norway. The project has two major parts: 1) a summary of the literature on the field and 2) a proposal of how to follow-up women following preeclampsia, in order to reduce risk and severity of cardiovascular disease later in life.

My supervisor has been Professor Annetine Staff, University of Oslo and Oslo University Hospital. She is the head of the Research Center of Obstetrics and Gynecology at Oslo University Hospital, Ullevål. She has given me excellent support and guidance through the process of this project.

2 Abstract

Objectives: To review the literature about preeclampsia and other placenta related disorders in relation to future maternal cardiovascular health, and secondly propose a possible follow-up strategy.

Material and Methods: This student project used a non-systematic literature research in PubMed and in McMaster PLUS. Articles were selected in agreement with my supervisor Professor Annetine Staff, who also supplied me with some clinical guidelines and additional reviews and studies. Search terms included “placenta, preeclampsia (HELLP/eclampsia), fetal growth restriction, intrauterine/fetal growth restriction/retardation, SGA (small for gestational age), placental insufficiency, abruption placenta”, combined with the keywords “CVD, stroke, atherosclerosis, myocardial infarction, hypertension, cerebrovascular disease”. Another search also included the keywords “acute atherosclerosis and CVD”.

Results: Preeclampsia and other placenta related pregnancy complications increase the risk of subsequent coronary heart disease, stroke and CVD in general (risk estimates between 1.3 to 3.3). The association is further increased with the severity of preeclampsia. Preeclampsia combined with preterm birth, IUGR, fetal death or recurrent disease increases the risk to 2.8-8.1, compared with the risk of women with uncomplicated pregnancies. Also there seems to be a dose-response relationship between the CVD risk and recurrent preeclampsia: the risk increases with recurrence.

Conclusions: Women experiencing preeclampsia and other placenta related pregnancy complications have a substantially increased risk of future cardiovascular disease. At present, there is no agreed follow-up program of these women after pregnancy. This student project proposes a Flow Chart with follow-up preventive measures in order to reduce the risk and burden of long-term CVD among these parous women with elevated CVD risk. The author of this student project proposes the group of parous women affected by early onset or recurrent preeclampsia to be offered an intensified long-term follow-up and assessment.

3 Background

Cardiovascular disease (CVD) is a major threat against women's health, and is still the leading cause of mortality among women in Norway (1) and globally (2).

Preeclampsia and other placenta-related pregnancy complications are shown to have a strong association with the development of cardiovascular disease later in life (15) (22). Although most of the pathology evolving during preeclampsia is resolved after delivery, several studies have found that women with preeclampsia are at high risk of developing cardiovascular disease later in life (3). Large studies with long-term follow-up report an increased risk of stroke (4), type 2 diabetes (5) and ischemic heart disease (6) later in life following a preeclampsia pregnancy.

Although the absolute increase in numbers of women developing cardiovascular disease after preeclampsia may be limited, the implication to women's health may be fatal, as myocardial infarct, cerebral stroke and death are among the possible outcomes. There is still discussion as to whether there is causality between these two conditions or whether the association is merely due to a shared common disposition of risk factors. Either way, women who have developed preeclampsia are at increased risk of developing cardiovascular disease later in life compared to women with uncomplicated pregnancies. Hence, there are arguments supporting that these women should be followed up after delivery; similarly to other high-risk groups that are followed up to prevent future disease. By follow-up of this group of women, and by targeted prophylaxis and intervention, the cardiovascular mortality could possibly be reduced to an even greater extent than it is today. Offspring health after placenta-related pregnancy complications may also be affected, but this topic is not the focus of the present student project.

My aim with this project is consequently to review the literature of the evidence that associates CVD and placenta-related complications of pregnancy such as preeclampsia. Further I will suggest a rational clinical follow-up after such pregnancy complications, based on published literature as well as guidelines by the American Heart Association (41). In addition my supervisor has provided me the NICE guidelines (18) and revised guidelines from the Norwegian Gynecological Association (NGF) (43), the latter to be published in 2014.

4 Methods

This student project used a non-systematic literature research in PubMed and in McMaster PLUS. A search strategy was performed where articles with focus on maternal health after pregnancy complications were included. Primary outcome were cardiovascular diseases. Other maternal health issues such as increased diabetes risk, reduction of breast cancer and other connected conditions have been excluded from the search. Articles were selected in agreement with my supervisor Professor Annetine Staff, who also supplied me with some clinical guidelines and additional reviews and studies.

Search terms included “placenta, preeclampsia (HELLP/eclampsia), fetal growth restriction, intrauterine/fetal growth restriction/retardation, SGA (small for gestational age), placental insufficiency, abruption placenta”, combined with the keywords “CVD, stroke, atherosclerosis, myocardial infarction, hypertension, cerebrovascular disease”. Another search also included the keywords “acute atherosclerosis and CVD”.

Case-control and cohort studies up to July 2013 were included, as well as meta-analysis and systematic reviews. Studies prior to 2001 were excluded, due to the restricted time available for the student project, as well as articles published in other languages than English. Some particularly interesting studies (even prior to 2001) have been selected through an additional extended search. I have primarily selected human studies, although some few animal studies have been included as well.

Abstracts have been read and papers have been selected in agreement with my supervisor Annetine Staff, who has an extensive research background and knowledge in this field.

5 Results

5.1 Definitions

5.1.1 Preeclampsia

The current definition of preeclampsia is well debated, as it defines a syndrome with heterogeneous pathophysiology and clinical outcome, but there is general consensus to include the criteria of new onset of hypertension and proteinuria in the second half of the pregnancy (7). Preeclampsia is a syndrome including several features, both maternal and fetal. The pathogenesis is still unclear, but some characteristic components such as increased oxidative stress, genetic variance and placental and immunologic factors contribute on various pathophysiological levels in the process (9). Staff et al recently called for a renewal of the definition, which has been unchanged despite new evidence and a greater understanding of the disease (10). In the future, preeclampsia definition, prevention and follow-up may also involve longitudinal assessment of circulating biomarkers that may better identify subgroups within the larger and more heterogeneous preeclampsia group (10).

The American College of Obstetricians and Gynecologists defines preeclampsia as de novo hypertension $>140/90$ mm Hg and proteinuria >0.3 g per 24 hours after 20 weeks of gestation (11). The definition is now under revision (10). A broader approach in order to include the heterogeneity of preeclampsia has been acknowledged in Australia and by the Society of Obstetricians and Gynecologists of Canada. The extended definition additionally includes (≥ 1) new fetal or maternal features such as fetal growth restriction (FGR), hepatocellular dysfunction or renal insufficiency (12).

During placentation, mononuclear extra villous fetal cytotrophoblasts invade between week 8 and 18 the placental bed and its uteroplacental spiral arteries (10). The invasion occurs either interstitially or via the blood vessels into the decidual lining (which is the endometrium in pregnancy) and the inner third of the myometrium (9). The spiral arteries are in normal pregnancy extensively remodeled in the segments of the inner myometrium and terminal decidua. The remodeling mainly constitutes of loss of smooth muscle and extensive dilatation and reduces the velocity, pressure and pulsatility of the utero-placental blood flow (10).

In preeclampsia, the endovascular trophoblast invasion into the spiral arteries is restricted to the peripheral parts of the decidua. The remodeling is incomplete and the spiral arteries remain more constricted and thick-walled than in a normal pregnancy (10). Retention of vasoactive smooth muscle in the vessels might lead to intermittent flow and subsequent dysfunctional villous flow and placental increased oxidative endoplasmic reticulum (ER) stress as a result (13). The current understanding is that this placental stress stimulates release of trophoblast-derived factors into the maternal circulation, which again contributes to the exaggerated maternal inflammatory response that characterizes preeclampsia (14). In addition, there may be many factors provoking or contributing to dysfunctional placentation: genes (including paternal genes), thrombophilia, pre- gestational hypertension and chronic renal disease (15).

Interestingly, many pregnancies complicated by preeclampsia are also affected by acute atherosclerosis in the uteroplacental spiral arteries. These lesions resemble early stages of atherosclerosis, and usually affect the most peripheral parts of the already poorly remodeled spiral arteries seen in preeclampsia. Acute atherosclerosis is not unique for preeclampsia, but is also seen in other conditions such as IUGR, systemic lupus erythematosus and antiphospholipid syndrome (9). There are at present no studies that have been able to link acute atherosclerosis of pregnancy and subsequent CVD or atherosclerotic disease, although this has been suggested by Staff et al, and is currently under investigation (9)(10)(16). Staff and coworkers have proposed that presence of uteroplacental acute atherosclerosis might target women at highest risk of premature atherosclerotic cardiovascular disease and that these vascular diseases may have common pathophysiological features, including vascular inflammation (16).

5.1.2 Early-onset vs. late-onset preeclampsia

Preeclampsia has been stratified into two broad types based on the placental and maternal pathophysiological characteristics, although they are incompletely clinically defined and recognized. *Maternal preeclampsia* dominated by maternal features occurs where the mother has predisposing conditions of systemic inflammation, such as diabetes mellitus, chronic hypertension, obesity, or autoimmune disorders. This pre-inflammatory state may lead to an abnormal reaction of her vessels in pregnancy. Hence, clinical signs of preeclampsia may evolve even if the placentation process has been normal (16). On the other hand there is the *Placental preeclampsia* with placental

features such as IUGR, preterm delivery and even potentially fetal death dominating the clinical and pathophysiological picture of the syndrome. The placental preeclampsia form is proposed to evolve in a three stage model according to Redman et al: 1) lack of remodeling of spiral arteries and poor placentation, 2) consequent dysfunctional perfusion, dysfunctional placenta function, increased placental and systemic oxidative stress, 3) development of clinical features, which may include fetal growth restriction and early-onset disease (17).

This leads to another, but similar sub classification into early- and late-onset preeclampsia, which is already widely used clinically today (10). The *early-onset preeclampsia type* seems to correspond to the *placental preeclampsia type* and likewise the *late-onset preeclampsia type* seems mainly to correspond to the *maternal preeclampsia type*. Although the general accepted clinical classifications of preeclampsia do not differ between these two possible subtypes, there are several studies with results pointing in the direction of two different conditions with different phenotypes and etiologies. Early-onset preeclampsia usually includes a delivery before week 37, although many researchers use gestational week 34 as a threshold, as it better identifies women with the more severe outcomes both on short- and long-term. The majority of women with preeclampsia is however delivered after week 37 and hence has a less severe type (19), although the much feared eclampsia complication may kill a women (and her offspring) at term and even in post-term preeclampsia.

5.1.3 Small for Gestational Age (SGA) and Intrauterine Growth Restriction (IUGR)

Small for gestational age (SGA) babies occurs in 20-25% of preterm births and in 14-19% of term births complicated by preeclampsia (18). The condition is mainly due to fetal growth restriction arising from placental disease. It may be defined as newborn weight being less than the tenth centile (and sometimes as less than the 3rd and 5th centile) for the gestational age for the whole population.

IUGR (intrauterine growth restriction) is also named fetal growth restriction (FGR) and is not equivalent to SGA, as IUGR /FGR defines a pregnancy where the fetus is not reaching its growth potential. IUGR / FGR has been defined differently in many studies, and may be more difficult to diagnose than a SGA diagnosis. A SGA pregnancy can have other causes than IUGR / FGR, and not all IUGR / FGR pregnancies result in a SGA outcome. Both conditions may however be used as a proxy for placental dysfunction,

although a SGA baby can be due to genetic conditions or even due to ethnical variations without any pregnancy pathology.

5.2 Epidemiology: Cardiovascular disease and preeclampsia

Preeclampsia occurs in 3-7% of all pregnancies and is a potentially lethal pregnancy condition for the mother in a global perspective. Especially is the risk of severe complications high in developing countries with suboptimal pregnancy follow-up. Even in countries with advanced pregnancy care, such as the UK, handling of severe cases may be suboptimal. Four women died from preeclampsia/eclampsia in UK between 2003-2005. Poor anesthetic management contributed to these deaths (18).

In a more long term perspective, preeclampsia is not only potentially lethal during the actual disease, but also it has recently become clear that women who have had preeclampsia are at substantially increased risk for cardiovascular disease later in life and premature death compared to women with healthy pregnancies (16).

Large population-based studies from Scandinavia and UK agree on the association between preeclampsia and future CVD: A Norwegian register based study cohort by Irgens et al studied the long-term mortality of mothers and fathers after preeclampsia. Approximately 600 000 births of fathers and primiparous women were included between 1967 and 1992. The study showed an eight-fold higher risk of deaths of cardiovascular causes among women who had preeclampsia and preterm delivery compared to the reference group of women with term pregnancies without preeclampsia (7). The study also found a 1,65-fold increased risk of dying from cardiovascular disease among mothers who had preeclampsia and a term delivery. The findings were consistent with a reduced survival in mothers with both preterm delivery and preeclampsia over the 25 years of follow-up (7).

Likewise, in a large meta-analysis and systematic review in the UK, Bellamy et al found that women with a history of preeclampsia have approximately double the risk for subsequent ischemic heart disease, stroke, and venous thromboembolic events over the 5 to 15 years after pregnancy. The meta-analysis included 25 cohort studies and approximately 3.5 million women, of whom 198 252 had preeclampsia and over 3 million did not (4).

Moreover a large Scottish population based cohort study by Smith GC et al (6) assessed whether pregnancy complications according to low birth weight were associated with the mothers' future risk of developing ischemic heart disease. They found a doubled risk for admission to hospital or death due to ischemic heart disease if the woman had preeclampsia during her pregnancy compared to women without preeclampsia. In addition they found a seven-fold increased risk of ischemic heart disease if the woman had preeclampsia and delivered a baby in the lowest birth weight quintile (under 2.5 kg). Their findings were adjusted for maternal age, maternal height, socioeconomic deprivation category and essential hypertension.

5.2.1 The association with CVD strengthens with severity of preeclampsia

The association between preeclampsia and subsequent cardiovascular mortality and morbidity strengthens with more severe preeclampsia, including early onset, recurrent disease, and neonatal morbidity:

In a large Scandinavian population based cohort study, Lykke et al (5) assessed whether mild and severe preeclampsia were associated with subsequent cardiovascular endpoints among mothers delivering in Denmark over a period of 30 years. Depending on the severity of preeclampsia, they found a three- to six-fold risk for subsequent hypertension. With recurrent / severe preeclampsia, the risk was increasing (5). Staff et al suggests that there seems to be a “dose response” relationship between future cardiovascular disease and the severity of preeclampsia (16). A similar significant effect was noted according to other measured cardiovascular outcomes, such as ischemic heart disease, congestive heart failure, stroke and diabetes mellitus type 2 (5).

Similarly a review by Newstead et al found the risk for coronary heart disease, stroke, and other cardiovascular events to be highest among women who develop both maternal signs of preeclampsia (e.g. hypertension and proteinuria) in addition to abnormal placentation (e.g. fetal growth restriction). The risk was especially high with preterm delivery (15). Likewise Lykke et al found that preterm delivery in addition to preeclampsia leads to a higher risk of subsequent hypertension, ischemic heart disease, congestive heart failure, and diabetes mellitus type 2, compared with women having preeclampsia and delivering at term (5).

Bellamy et al observed correspondingly that women who had early-onset preeclampsia had the greatest risk of future cardiovascular disease and the risk was higher in this

group than in those who had severe preeclampsia, the latter defined as blood pressure exceeding 160/110 mm Hg and/or proteinuria greater than 5 g/24 h (4).

A Swedish population based study by Wikström et al found additionally that recurrent preeclampsia strengthens the association with subsequent CVD compared to preeclampsia only in the first pregnancy. In their cohort study, including more than 20000 hypertensive primigravida and 2000 women with recurrent hypertensive disease, they found an increased risk of hospitalization for or death from ischemic heart disease both in women with recurrent and non-recurrent hypertensive pregnancy disease. But the risk was higher when the hypertensive disease was recurrent and it also increased with severity (21). Furthermore pregnancy complications such as hypertensive disease, preterm delivery and SGA were found to have an independent impact on the risk of developing ischemic heart disease later in life, equivalently to the findings in previous mentioned studies. The highest risk of developing ischemic heart disease was in women with recurrent hypertensive disease with a risk ratio of 2.8 compared with 1.9 when the woman were having hypertensive disease only (21).

Further a Canadian cohort study by Ray et al noted a doubling of the risk of premature cardiovascular disease in women with previous maternal placental syndromes during pregnancy compared with those who had not. Maternal placental syndromes were defined as preeclampsia, gestational hypertension, placental abruption or placental infarction in their study. This risk was further increased by the combined presence of a maternal placental syndrome and fetal growth restriction (three-fold) or intrauterine fetal death (four-fold). Also pre-existing risk factors for cardiovascular disease such as metabolic syndrome and tobacco use were shown to increase the risk of premature cardiovascular disease, relative to neither (22).

5.3 Potential mechanisms: CVD and preeclampsia – a common pathophysiology?

In support of a common causal link, obesity, hyperlipidemia, hypertension, and other disorders associated with pre-existing endothelial dysfunction, such as diabetes mellitus are risk factors shared by women at risk of both preeclampsia and cardiovascular disease (23).

It is still not clear whether the augmented risk of cardiovascular disease are present before the initiation of the pregnancy, or if these risk factors have developed during or after pregnancies complicated with preeclampsia. This major question has to be examined further by longitudinal studies, where women are included prior to pregnancy. Such a retrospective study was performed recently in Norway by Magnussen et al (24), who found increased metabolic risk factors such as total serum cholesterol, triglycerides and glucose, also prior to pregnancy in women developing preeclampsia. They also found a positive association of pre-pregnancy systolic blood pressure with the risk of preterm birth (OR 1.7) compared with normotensive women (24).

Dyslipidemia and relative glucose intolerance may be a marker for an atherogenic profile that may predispose women to both preterm birth (e.g. due to preeclampsia) and atherosclerosis (24). Histopathological similarities found in placentas of preeclampsia, IUGR, and preterm deliveries may suggest a common pathophysiologic pathway (25)(26). We now know that the risk of cardiovascular disease is higher in women with a history of preeclampsia and in women who have experienced preterm delivery or the delivery of an IUGR infant (6)(7). Magnussen et al suggest that maternal risk factors for cardiovascular disease, such as dyslipidemia and glucose intolerance, may also provide a link to the risk of preterm births. Their findings indicate that unfavorable levels of serum lipids, blood pressure, and glucose may contribute to the risk of preterm birth, and that preterm birth and cardiovascular diseases may share common risk factors for cardiovascular disease (24).

Although the literature indicates that pre-gestational risk factors for preeclampsia such as obesity, insulin resistance, inactivity, diabetes mellitus, hypertension, inflammation, family history etc. are similar to the risk factors for CVD, an important paradox is smoking. There is discordance between the protective effect of smoking on risk of preeclampsia and its contribution to the elevated risk of cardiovascular disease (27). Smoking is associated with an augmented risk of atherosclerosis and CVD, but a reduced risk of preeclampsia. Hence, smoking is a divergent risk factor according to CVD and preeclampsia. However, the relation between smoking and acute atherosclerosis is unknown (16).

5.3.1 Pregnancy as a stress test for future maternal health

Because of its unique cardiovascular and metabolic stress, pregnancy provides a unique opportunity to estimate a woman's lifetime risk for future cardiovascular health.

Pregnancy is said to be a "mini "stress test of the cardiovascular system. If preeclampsia and cardiovascular disease share a common pathophysiology, then preeclampsia could be seen as an early stage on the path to clinical cardiovascular disease. The hypothesis is that maternal endothelial dysfunction is a condition that exists prior to manifestation of clinical preeclampsia, and that the metabolic stress of a pregnancy predisposes these women with endothelial dysfunction to develop preeclampsia. With increasing age the endothelial dysfunction can develop into a manifest cardiovascular disease (21).

Two theories are discussed regarding the epidemiological association between preeclampsia and cardiovascular disease (16). The first is that preeclampsia and atherosclerosis, including cardiovascular disease in general, have common risk factors for systemic inflammation, which are unmasked by the "stress" of pregnancy. Such factors include obesity, dyslipidemia, diabetes, insulin resistance, high blood pressure, endothelial dysfunction and a family history (9). In contrast to preeclampsia dominated by placental features, maternal preeclampsia is not necessarily associated with abnormal placentation and inadequate perfusion (10). Maternal endothelial dysfunction is already present, because of preexisting vascular dysfunction, and is further exacerbated as a result of the physiological burden of pregnancy (28).

5.3.2 Genes and environment

Common environmental factors for preeclampsia and future cardiovascular disease may possibly include physical inactivity and an atherogenic diet. In a prospective cohort study including 3133 pregnancies in Norway, Clausen et al found that high intake of energy, sucrose and polyunsaturated fatty acids early in the second trimester may increase the risk for preeclampsia; especially a marked effect was seen concerning early-onset preeclampsia (29). In another prospective cohort study Clausen et al found a dose/response relationship between body mass index and increased risk of pregnancy complications. Further overweight was shown to be a strong independent predictor of pregnancy complications (30).

Also, common predisposing factors for preeclampsia and CVD may include genotypes that are shown to have both risks for hypertension in the general population, as well as

risk for preeclampsia in the fertile population. Such an example is the study from Norway, by Kvehaugen et al (31), showing increased risk for preeclampsia and acute atherosclerosis among women with a polymorphism of the regulator of G protein signaling (RGS2) gene (31). This RGS2 gene has previously been shown to be associated with hypertension. Kvehaugen et al suggest that the possible mechanisms might be through dysfunctional signaling through the renin angiotensin system, which is an important controller of human blood pressure.

5.3.3 Pregnancy as a mediator for future CVD

The perspective of looking at the pregnancy as a mediator, which may increase risk of future cardiovascular disease, does not exclude a common pathophysiology, but pregnancy could be an additional risk factor. A normal pregnancy without preeclampsia involves several physiological and metabolic changes, which may be exaggerated in a preeclamptic pregnancy. A woman experiencing a normal pregnancy is exposed to several months of a hyperlipidemic state. This hyperlipidemia is even more profound in a preeclamptic pregnancy and might induce long-term damage to the vascular wall (16). In addition, a dysfunctional placenta sheds even more bioactive substances than a placenta from an uncomplicated pregnancy. This results in dysregulated circulating factors with unknown effects of the systemic vasculature on a long-term basis, including more antioangiogenic and less proangiogenic proteins (10). In line with placenta and pregnancy inducing long-lasting effects and risk for CVD, Staff et al propose a hypothesis of an indirect pathway to cardiovascular disease due to damaged or depleted endothelial vascular progenitor stem cells (16).

5.4 Major cardiovascular atherogenic diseases after preeclampsia

5.4.1 Hypertension

Many large epidemiologic studies found evidence for subsequent hypertension after preeclampsia. Lykke et al found an over three-fold increased risk of subsequent hypertension after mild preeclampsia, and over six-fold increase after severe preeclampsia. Compared with women without preeclampsia, women with preeclampsia had a four-fold risk of future hypertensive disease. Furthermore they found that not only the severity of the preeclampsia but also the parity and recurrence of preeclampsia

affected the risk of developing subsequent cardiovascular disease. Women with two preeclamptic pregnancies had as much as a six-fold increased risk of developing future hypertension compared to women with preeclampsia only in their first pregnancy (three-fold risk). Severe preeclampsia in a primiparous woman was increasing the risk of subsequent hypertension by eight times compared to women with no hypertensive disorders. In addition, the risk of subsequent hypertension increased to nine-fold if preterm delivery. If preeclampsia and SGA, the risk was four-folded. Eventually, an additive effect was shown with an over seven-folded risk if preeclampsia was accompanied by preterm delivery and the baby was small for gestational age (5).

Also Bellamy et al showed an almost four-fold increased relative risk of future hypertension in women with previous preeclampsia compared to women without preeclamptic pregnancies in their history. Preeclampsia in any pregnancy compared with preeclampsia in only the first pregnancy was associated with an even greater relative risk of future hypertension. According to parity, the analysis indicated a higher relative risk of hypertension after preeclampsia in any pregnancy compared with preeclampsia in the first pregnancy only (4).

Furthermore the analysis of Bellamy et al (4) included findings of an almost four-fold increased risk of later diagnosis of hypertension in women with previous preeclampsia compared to women without preeclamptic pregnancies in their history. Also preeclampsia in any pregnancy compared with preeclampsia in only the first pregnancy was associated with an even greater relative risk of future hypertension. The authors therefore concluded that it is likely that women with recurrent preeclampsia have an underlying pathological phenotype, which may cause the increased risk of developing hypertension and cardiovascular disease.

Magnussen et al (32) report a higher systolic and diastolic blood pressure in women with previous preeclampsia compared to women without. Following this, women with preeclampsia were three times likely to use blood pressure medication at follow-up, compared to women without any history of preeclampsia (32).

5.4.2 Ischemic heart disease

Over 2 million women in the meta-analysis of Bellamy et al contributed to the analysis of fatal and non-fatal ischemic heart disease. The relative risk of having a fatal event of ischemic heart disease was found to be nearly three-folded. The weighted mean follow-

up was 11.7 years. The risks of ischemic heart disease were approximately two-folded and similar both for primiparous women with preeclampsia and for women with preeclampsia in any pregnancy. Preeclampsia before 37 weeks gestation was found to be associated with nearly an eight-fold increased risk of ischemic heart disease compared with women with normal blood pressure delivering at term (after 37 weeks' gestation) (4).

5.4.3 Cerebrovascular disease /stroke

In the review of Bellamy et al, approximately 1.5 million women contributed to the analysis of stroke. 64 551 women had preeclampsia and 907 incidents of stroke were noted among these. The mean weighted follow-up was 10.4 years. The overall risk of fatal and non-fatal stroke after preeclampsia was almost two-folded compared with women who did not develop preeclampsia (4). Irgens et al found that mothers with preeclampsia and preterm delivery were found to have a five-fold increased risk of dying from stroke (3).

5.4.4 Cardiovascular biomarkers and endothelial dysfunction after preeclampsia

A recent Norwegian study by Sugulle et al (33) found that a precursor of the atrial natriuretic peptide (MR-proANP) was increased in women during preeclamptic pregnancies. The concentrations were at the same levels as in patients with acute ischemic stroke, and were hypothesized to reflect the massive hemodynamic stress in preeclampsia. There were however no differences between the preeclamptic and the normotensive women concerning the maternal circulating concentrations in a follow-up study 5 to 8 years later (33).

This is in contrast to another publication from the same research group; demonstrating elevated antioangiogenic soluble Flt1 (sFlt1) concentrations in mothers 5 to 8 years after a preeclampsia delivery (34). The authors also found evidence of reduced arterial reactive hyperemia index in women (and offspring) after preeclampsia and delivery of a SGA baby (34), as well as possible indication for early cardiac dysfunction in the offspring, investigated by cardiac tissue Doppler examination (35).

5.4.5 Insulin resistance

The risk of subsequent diabetes mellitus type 2 was found to be two-folded increased after hypertensive pregnancy disorders in the study by Lykke et al. Severe preeclampsia

raised the risk somewhat more (3.68). Adjustment for relevant factors, such as family income, smoking, and BMI attenuated the estimate of the association by 18% (5).

Magnussen et al (32) reported in a large cohort study of more than 15 000 women in Norway a nearly three-folded risk for diabetes following a preeclamptic pregnancy. This was only marginally attenuated after adjustment for BMI.

5.4.6 Serum lipids

In the Norwegian study by Magnussen et al (32), an increased level of triglycerides, total serum cholesterol and LDL cholesterol, together with lower levels of HDL cholesterol was found two decades after PE pregnancies.

Further data from different cohort studies are shown in the table below:

Table 1 Retrospective cohort studies linking preeclampsia and subsequent cardiovascular disease: adjusted RR for different types of outcome.								
Authors		Outcome		Preeclampsia combined with preterm delivery	Severe or recurrent preeclampsia	Combined with IUGR/FGR	N. of women included in the study	Duration of follow-up period (years)
	Cardio-vascular disease	Cerebro-vascular disease	Hyper-tension					
Smith et al 2001 (6)	1.3				7.0		783 340	20.4
Lykke et al 2009 (5)					6			
Bellamy et al 2007 (4)	2.16	1.81	3.7	7.1				≈12
Wikström et al 2005 (21)	2.1			2.6	3.1		403 550	15
Ray et al 2005 (22)	2.1	1.9				3.1	1.03 million	8.7
Irgens et al 2001 (6)	1.6			8.1			626 272	13
Skjærven et al 2012 (36)	1.6			3.7			836 147	
Kestenbaum et al 2003 (37)	2.2				3.3		807 010	7.8
Wilson et al 2003 (38)		2.1					3593	15-19
Männistö et al 2013 (39)	1.4		2.33				12 055	34.9

6 Follow-up after preeclampsia for CVD risk

Pregnancy complications such as preeclampsia can give health caretakers the opportunity to identify young women with increased risk for developing cardiovascular disease later in life. This would enable us to set up targeted programs for the follow-up of these women and to introduce and assess prevention strategies on an early stage in targeted groups at highest risk. This could prevent or postpone CVD risk and reduce long-term burden and detrimental health consequences for this group of young women. Such a follow-up program would be of great importance since a major part (90%) of myocardial infarctions in women are attributed to modifiable risk factors (42).

6.1 Pre-existing guidelines and recommendations

6.1.1 The American Heart Association (AHA)

Recent guidelines published by the American Heart Association (AHA) have included a pregnancy complicated by preeclampsia and/or delivery of an IUGR child as an additional risk factor for cardiovascular disease (41). A history of preeclampsia is listed as a major risk factor equally with metabolic syndrome, obesity, cigarette smoking, hypertension, advanced subclinical atherosclerosis etc. AHA further advises that women, who develop hypertensive disorders during pregnancy, should be referred to a cardiologist or primary care physician to enable further assessment and reduction of cardiovascular risk profile. By referral of these women, risk factors can consequently be monitored and controlled in an appropriate manner in the years after pregnancy. AHA has also called for a renewal of lifestyle advices and cholesterol lowering and anti-hypertensive medication (41).

6.1.2 The NICE guidelines

Until recently there has been no guidance on the assessment and care of women after a pregnancy complicated by preeclampsia or other placenta related pregnancy complications in the UK. However, in 2010, The NICE guidelines were published and some recommendations were given:

All women who have had preeclampsia should be offered a medical review at the postnatal review 6–8 weeks after the birth (18). The women and their primary care clinicians should further be informed about the long-term risk of cardiovascular disease

and that preeclampsia is associated with an increased risk of developing high blood pressure with subsequent complications later in life (18).

6.1.3 The Norwegian Gynecological Association (NGF)

Guidelines for clinical follow-up after hypertensive pregnancies and eclampsia are also about to be published in Norway by NGF, the Norwegian Gynecological Association (43):

These guidelines recommend follow-up depending of the severity of preeclampsia and the risk of recurrence or future cardiovascular disease. If the woman (without known chronic hypertension) has hypertension when submitted from hospital, further control by general practitioner (GP) or hospital (obstetrician) should be set up (43). At 2-3 months after delivery, NGF recommends a general postpartum control at the GP, or at the delivery department, the latter if severe preeclampsia, eclampsia, HELLP or adverse outcome. The control should include blood pressure measuring and urinary control (43). If chronic hypertension has developed ($>140/90$) in the fertile woman, referral to a cardiologist for further assessment should be considered according to the NGF (43). Eventually the NGF guidelines recommends that women with previous preeclampsia should be informed about lifestyle advices and proper nutrition in the aim of preventing future cardiovascular disease. In addition a peri-menopausal follow-up is recommended in order to provide early diagnosis and treatment (43).

6.2 Discussion / Perspectives

At postpartum follow-up after preeclampsia, clinicians today regularly provide information about risk of developing preeclampsia in a future pregnancy and clinical follow-up in next pregnancy. However, the information on future cardiovascular health is probably less routinely discussed with the patients, also because strict guidelines on follow-up systematic routines are lacking. Also, referral to cardiologists of all women after preeclampsia, would be neither cost-effective nor achievable globally or even in Norway.

The missing standardized follow-up regime is reflected in health workers providence of health services to these women. A recent study of primary health care workers at a hospital in the US found that a major part of the physicians were unaware of the association between preeclampsia and future cardiovascular disease. Very few of these

health workers were giving advices about lifestyle modifications, aiming for reducing the risk profile among these women (44). Another recent study from Germany (45) found that although the majority of obstetrician-gynecologists were aware of increased risk of CVD among women with a history of preeclampsia, there were still weaknesses in the follow-up care and counseling of these patients (45). This is in line with the general situation in Norway and worldwide, even in affluent societies (A Staff, personal communication).

6.2.1 My own proposal of a Flow chart for follow-up after PE / Placental complication regarding CVD

Based on the findings presented above, and in cooperation with my supervisor Annetine Staff, I have suggested the following flow chart as an aid in tailoring individual follow-up of a woman after a preeclampsia delivery in Norway. If the hypothesis of Staff and coworkers are confirmed in the future (16), showing that women with uteroplacental acute atherosclerosis have higher risk of CVD, irrespective of a preeclampsia diagnosis or not, women with a acute atherosclerosis diagnosis postpartum could be offered more intensified follow-up than women without these vascular affections. Presently, immunohistochemical acute atherosclerosis diagnosis is not part of a routine diagnosis after delivery of placenta.

A routine cervical screening is offered every third year to all Norwegian women at 25-67 years of age, most often performed by the general practitioners. We suggest an expansion of this routine screening to also include blood pressure measuring in women with previous preeclampsia (PE) or other placenta-related pregnancy complications such as FGR. This expansion will not constitute a major alternation in the use of public health resources. After the age of 67, the public cervical screening is terminated. At the same time the risk of CVD is increasing along with increasing age, and we therefore suggest an implementation of yearly blood pressure measuring after age 67, depending on total risk factors (see chart) in order to achieve an adequate follow-up and reduce the risk of cardiovascular morbidity and mortality among these women.

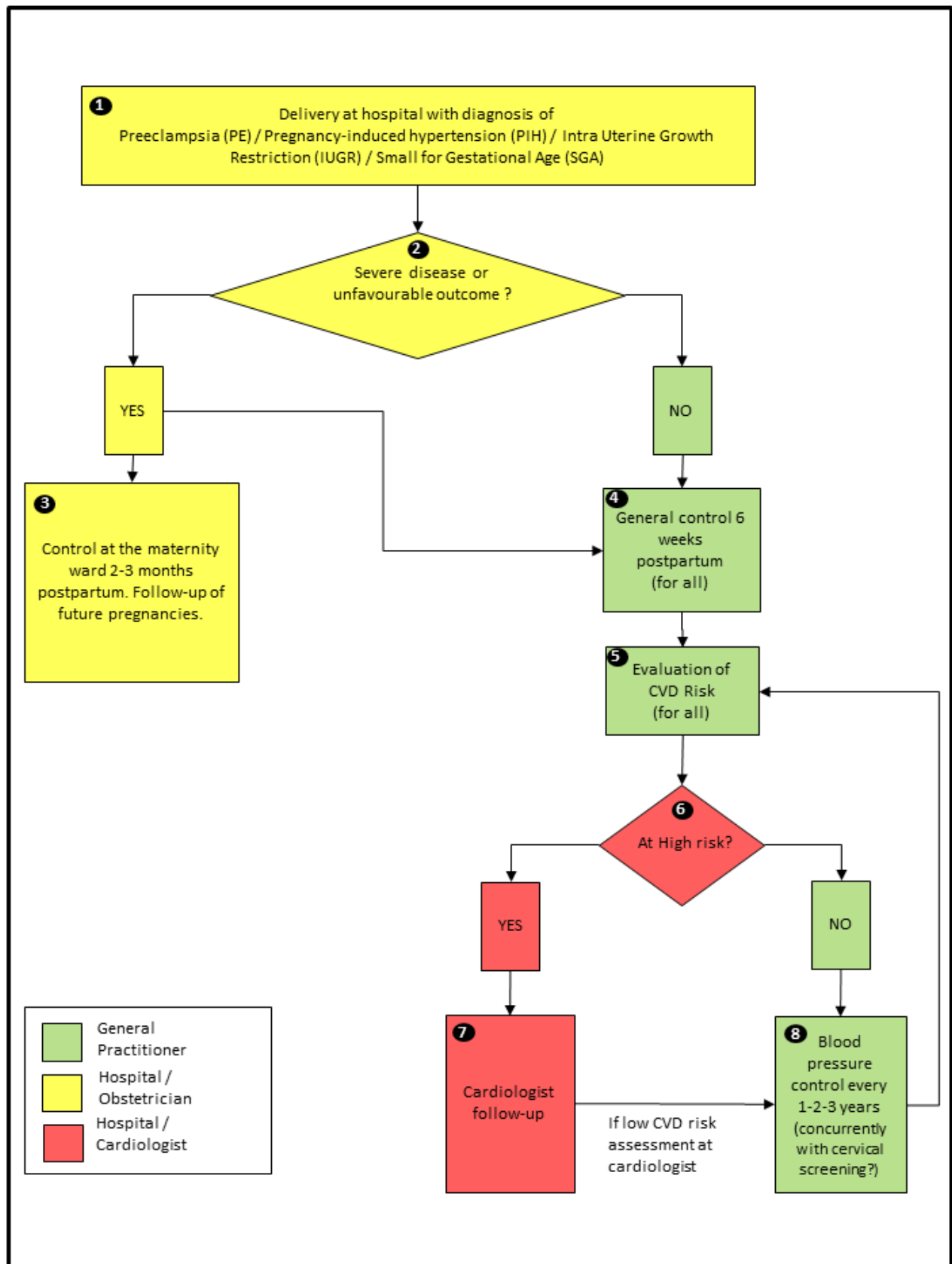
Another aspect to considerate is the use of the Norwegian NORRISK calculator (40) in order to estimate a patient's current risk of future CVD. This calculator may however lead to an underestimate of the woman's risk, as the calculator is currently lacking a history of pregnancy complications as a risk factor for future CVD. Hence, the calculated

10-year risk of CVD turns out to be underestimated in women with previous pregnancy complications such as preeclampsia etc.

I propose this chart as an aid for the clinicians at the obstetric wards and for the general practitioners that will follow-up the preeclampsia patients on long-term basis. This chart would fit the public health system of Norway, as well as the one in UK, and may be modified in different societies with different traditions in providing health care to the general population and to populations at risk. A challenge is the balance between a potential beneficial positive prophylaxis effect on future CVD and the potential negative focus on poor health outcomes for women at risk, the latter potentially contributing to a reduced self-assessed quality of life in some women.

A one-pager of the flow chart is to be found in the appendix.

Flow chart for follow-up after PE and placental complications regarding CVD



No.	Description
1	Hospital in Norway.
2	E.g. severe hypertension $\geq 160/110$, extreme preterm delivery (<34 GW), eclampsia, HELLP, fetal death etc.
3	Follow-up by an obstetrician. Information on recurrent risk of preeclampsia in future pregnancies and option for acetylsalicylic acid prophylaxis from GW 12. Information on additional obstetrical follow-up in a next pregnancy.
4	GP 6-8 week postpartum control: Routine control includes Gyn. exam (routine), Blood pressure measuring, urinary control, assess unspecific* and pregnancy-specific** CVD risk, Information about the long-term risk of CVD and prophylaxis, weight control (exercise/calorie restriction). (**gestational diabetes mellitus, preeclampsia, preterm birth, or birth of an infant small for gestational age).
5	Includes medical history /family history /previous pregnancy complication history, physical examination (Blood pressure, BMI, waist size), lab. tests (incl. fasting lipoproteins, glucose), Framingham risk assessment if no CVD or diabetes.
6	High risk: if clinically manifest CHD, clinically manifest cerebrovascular disease, clinically manifest peripheral arterial disease abdominal aortic aneurysm, end-stage or chronic kidney disease, diabetes mellitus or 10-y Predicted CVD risk $\geq 10\%$ (a)
7	Cardiologist: Specialist assessments of CVD risk, including Echo cor, carotis artery evaluation etc. Reduction of cardiovascular risk profile, long-term follow-up and potential interventions (statins, antihypertensives etc.). If low risk assessment at cardiologist: referred back to GP for regular blood pressure controls.
8	At any GP routine control if previous PE pregnancy: Blood pressure measuring, urinary control, assess unspecific and pregnancy-specific CVD risk, information about the long-term risk of CVD and prophylaxis, weight control (exercise/calorie restriction).
	a) Mosca L et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American Heart Association Am Coll Cardiol. 2011 Mar 22;57(12):1404-23.
	* Medical history /family history /previous pregnancy complication history, Physical examination (Blood pressure, BMI, waist size), Lab. tests (incl. fasting lipoproteins, glucose), Framingham /NORRISK risk assessment if no CVD or diabetes.
	** Gestational diabetes mellitus, preeclampsia, preterm birth, or birth of an infant small for gestational age.

7 Conclusion

Women experiencing preeclampsia and other placenta related pregnancy complications have an increased risk of subsequent coronary heart disease, stroke and CVD in general (risk estimates 1.3 - 3.3). The association between preeclampsia and CVD is strengthened with more severe preeclampsia. Risk is highest among women who develop preeclampsia further complicated by preterm delivery, IUGR or fetal death (risk estimates 2.8-8.1). There seems to be a “dose-response” relationship between the CVD risk and recurrent preeclampsia: the risk increases with recurrence.

The literature provides the important base of evidence that is needed to be able to consider preeclampsia and other placenta-related disorders such as IUGR as a cardiovascular risk factor and to be able to set up a targeted follow-up and to offer a potential intervention program to a subgroup of these women. As we already know, many cardiovascular risk factors are modifiable. To prevent premature cardiovascular events it would be of great importance to perform follow-up programs for women with previous preeclampsia and other placenta-related pregnancy complications. Especially those with previously severe preeclampsia should be included for further targeted assessment and potential intervention.

Unfortunately, there are no published evidence-based guidelines for long-term management of women with previous preeclampsia without pre-existing cardiovascular risks markers. Based on the evidence in the literature and already published recommendations from AHA and UK, a simple flow chart of the follow-up procedures has been proposed in this student project. Using information from the pregnancy in parous women can assist in optimizing follow-up of these women. We could offer patient-tailored follow-up and potential pharmaceutical (such as statins, metformin etc.) or environmental (physical exercise, diet and weight control etc.) interventions to the patient groups at highest risk for CVD. Future longitudinal studies could assess whether such strategies would improve cardiovascular health and reduce the cardiovascular morbidity and mortality in a long-term perspective. This would be of great interest since cardiovascular disease is number one mortality cause also among women globally today and has detrimental effects on families and societies.

8 Litterature

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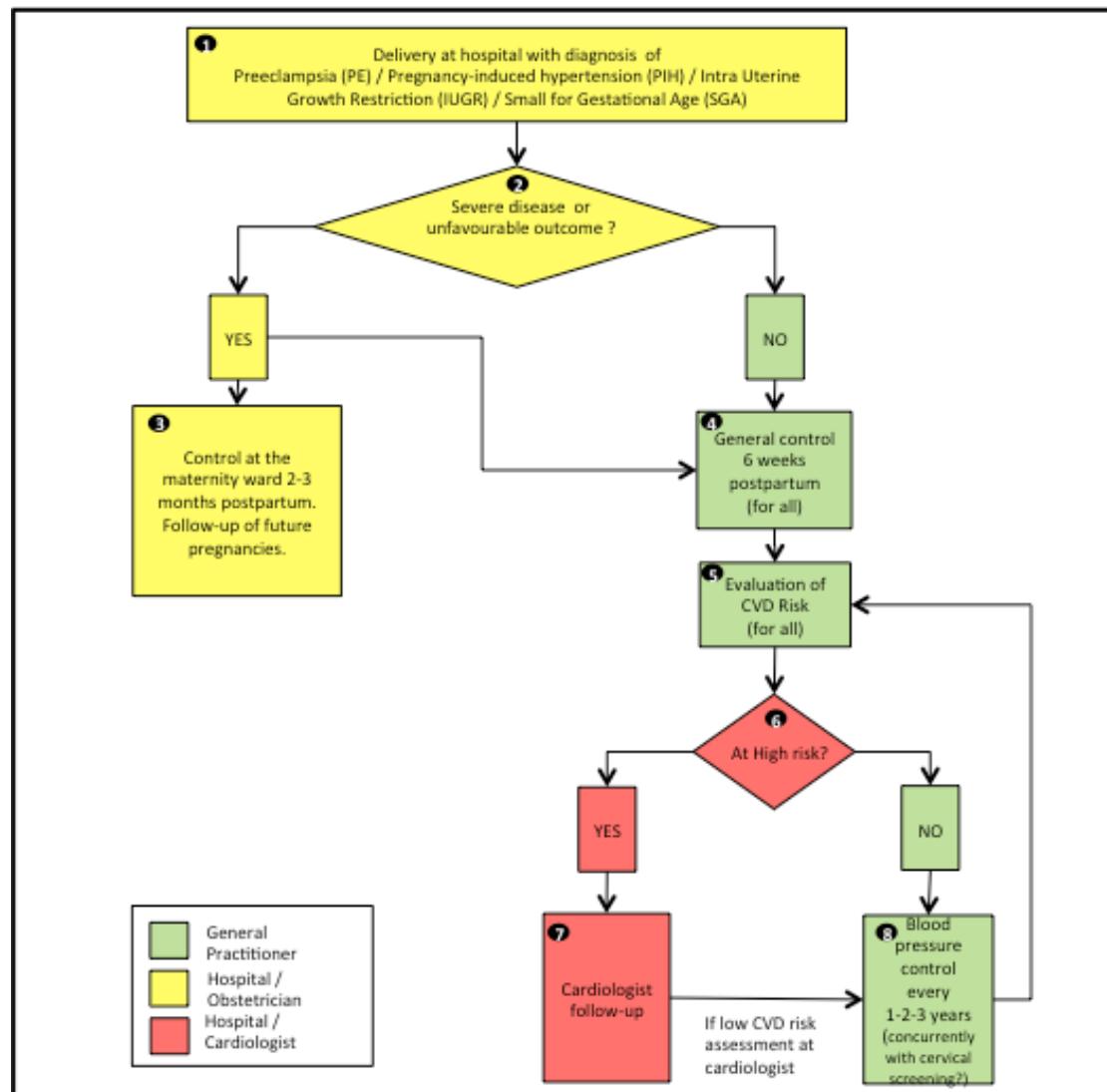
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9 Appendix

9.1 Flow chart



1. Hospital in Norway.
2. E.g. severe hypertension $\geq 160/100$, extreme preterm delivery (<34 weeks), eclampsia, HELLP, fetal death etc.
3. Follow-up by an obstetrician. Information on recurrent risk of preeclampsia in future pregnancies and option for acetylsalicylic acid prophylaxis from GW 12. Information on additional obstetrical follow-up in a next pregnancy.
4. GP 6-8 week pp control: Routine control includes Gyn. exam (routine), Blood pressure measuring, urinary control, assess unspecific* and pregnancy-specific** CVD risk, information about the long-term risk of CVD and prophylaxis, weight control (exercise/calorie restriction). (**gestational diabetes mellitus, preeclampsia, preterm birth, or birth of an infant small for gestational age).
5. Includes medical history /family history /previous pregnancy complication history, physical examination (Blood pressure, BMI, waist size), lab. tests (incl. fasting lipoproteins, glucose), Framingham risk assessment if no CVD or diabetes.
6. High risk: if clinically manifest CHD, clinically manifest cerebrovascular disease, clinically manifest peripheral arterial disease abdominal aortic aneurysm, end-stage or chronic kidney disease, diabetes mellitus or 10-y Predicted CVD risk $\geq 10\%$ (a)
7. Cardiologist: Specialist assessment of CVD risk, including Ecco cor, carotis artery evaluation etc. Reduction of cardiovascular risk profile, long term follow-up and potential interventions (statins, antihypertensives etc.). If low risk assessment at cardiologist: referred back to GP for regular blood pressure controls.
8. At any GP routine control if previous PE pregnancy: Blood pressure measuring, urinary control, assess unspecific and pregnancy-specific CVD risk, information about the long-term risk of CVD and prophylaxis, weight control (exercise/calorie restriction).

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* Medical history /family history /previous pregnancy complication history, Physical examination (Blood pressure, BMI, waist size), Lab. tests (incl. fasting lipoproteins, glucose), Framingham /NORRISK risk assessment if no CVD or diabetes.

** Gestational diabetes mellitus, preeclampsia, preterm birth, or birth of an infant small for gestational age.